REMARKS

For convenience, in the present response, Applicants will refer the Examiner to disclosure in the specification by referencing the appropriate paragraph numbers of the Substitute Specification that was submitted on May 3, 2002.

Status of the claims

Upon entry of the remarks and amendments, claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-350 will be pending in this application. Claims 281-350 have been added.

Claims 89, 98, 126, 140, 212, 221, and 230 have been amended. Applicants submit that the claims prior to amendments made herein were patentable and satisfied the requirements of 35 U.S.C. §§ 101, 102, 103 and 112. Applicants reserve the right to pursue the subject matter of the claims as recited prior to amendment herein in one or more continuing applications.

The word "therapeutically" has been deleted from claims 212, 221 and 230. The word "polypeptide" in claims 89, 98, 126, 140, 212 and 221 has been amended to "protein" because the term protein had antecedent basis in the claim.

In claims 212, 221, and 230, the words "modulates lymphocyte" have been replaced with the words "stimulates B lymphocyte." In claims 126 and 140, "lymphocyte" has been replaced with "B lymphocyte." New claims 281- 350 directed to methods of stimulating B cell proliferation, differentiation or survival or stimulating T cell proliferation differentiation by either administering proteins of the invention to an individual or contacting cells with proteins of the invention have been added. Support for these amendments may be found, for example, in the specification in paragraphs [0040], [0048]-[0051], [0077], [0153], [0156], [0300], [0620] and Examples 6 and 7.

Claims 89, 98, 212 and 221 have been amended to replace the phrase "modulates lymphocyte proliferation, differentiation or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Support for these amendments may be found, for example, in the specification in paragraphs [0331], [0342] – [0491] and Example 9.

No new matter has been added by way of amendment, and Applicants respectfully request entry of these amendments.

Objections to the Specification

In paragraph 3 of the Office Action mailed October 22, 2003, the Examiner objected to the Brief Description of the drawings for Figures 4A-4C for failing to make reference to the appropriate sequence identifier for the sequence of the HNEDU15 cDNA clone.

Applicants have amended paragraph [0060] to recite cDNA "clone HNEDU15" and to indicate that the nucleotide sequence obtained by sequencing the HNEDU15 clone is given in SEQ ID NO:1. Support for this amendment may be found in the specification as originally filed, for example in paragraphs [0023] and [0072] . Applicants submit these amendments address the Examiner's objections to the specification set forth in paragraph 3 of the Office action mailed October 22, 2003. Applicants respectfully request this objection be reconsidered and withdrawn.

In paragraphs 5-8 of the Office action mailed October 22, 2003, the Examiner has objected to the disclosure because the section entitled "Brief Description of the Drawings" refers to Figures 2C, 2D, 8C, 10C, 10D, 10E, 10F, 10G, 11D and 11F but, according to the Examiner, there are no such Figures in the application.

In response, Applicants draw the Examiner's attention to the Preliminary Amendment filed July 28, 2000 in which Applicants submitted 22 sheets of Formal Drawings containing each of the allegedly missing drawings. For the Examiner's convenience, copies of these 22 sheets of drawings as well as a copy of the date-stamped return receipt postcard indicating that these drawings were originally submitted to the United States Patent and Trademark Office on July 28, 2000 are submitted herewith. In view of the above, Applicants respectfully request that the Examiner withdraw the objections to the disclosure set forth in paragraphs 5-8 of the Office Action mailed October 22, 2003.

Amendments to the Claims:

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1-88. (Cancelled).

89. (Currently Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the ~~polypeptide~~ protein having said amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2~~modulates lymphocyte proliferation, differentiation, or survival~~.

90. (Previously Presented) The method of claim 89 wherein the protein comprises amino acid sequence (a).

91. (Previously Presented) The method of claim 89 wherein the protein comprises amino acid sequence (b).

92. (Previously Presented) The method of claim 89 wherein the protein comprises amino acid sequence (c).

93. (Previously Presented) The method of claim 89 wherein the protein also comprises a heterologous amino acid sequence.

94 (Previously Presented) The method of claim 93 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

95. (Previously Presented) The method of claim 89 wherein said protein is labeled.

96-97. (Cancelled)

98. (Currently Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the ~~polypeptide~~ protein having said first amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2~~modulates lymphocyte proliferation, differentiation, or survival~~.

99. (Previously Presented) The method of claim 98 wherein the protein comprises amino acid sequence (a).

100. (Previously Presented) The method of claim 98 wherein the protein comprises amino acid sequence (b).

101. (Previously Presented) The method of claim 98 wherein the protein comprises amino acid sequence (c).

102. (Previously Presented) The method of claim 98 wherein the protein also comprises a heterologous amino acid sequence.

103. (Previously Presented) The method of claim 102 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

104. (Previously Presented) The method of claim 98 wherein said protein is labeled.

105-106. (Cancelled)

107. (Previously Presented) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein consisting of the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

108. (Previously Presented) The method of claim 107 wherein the protein is fused to a heterologous amino acid sequence.

109. (Previously Presented) The method of claim 108 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

110. (Previously Presented) The method of claim 107 wherein said protein is labeled.

111-112. (Cancelled)

113. (Previously Presented) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

114. (Previously Presented) The method of claim 113 wherein the protein also comprises a heterologous amino acid sequence.

115. (Previously Presented) The method of claim 114 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

116. (Previously Presented) The method of claim 113 wherein said protein is labeled.

117-118. (Cancelled)

119. (Previously Presented) The method of claim 113 wherein the immunodeficiency is common variable immunodeficiency (CVID).

120. (Cancelled)

121. (Previously Presented) The method of claim 113 wherein the immunodeficiency is Selective IgA deficiency.

122-125. (Cancelled)

126. (Currently Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein consisting of a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of amino acid residues 134-285 of SEQ ID NO:2, wherein the ~~polypeptide~~ protein having said first amino acid sequence ~~modulates~~ stimulates B lymphocyte proliferation, differentiation, or survival.

127. (Previously Presented) The method of claim 126 wherein the protein consists of a first amino acid sequence which is 95% or more identical to said second amino acid sequence.

128. (Previously Presented) The method of claim 126 wherein the protein is fused to a heterologous amino acid sequence.

129. (Previously Presented) The method of claim 128 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

130. (Previously Presented) The method of claim 126 wherein said protein is labeled.

131-132. (Cancelled)

133. (Previously Presented) The method of claim 126 wherein the immunodeficiency is common variable immunodeficiency (CVID).

134. (Cancelled)

135. (Previously Presented) The method of claim 126 wherein the immunodeficiency is Selective IgA deficiency.

136-139. (Cancelled)

140. (Currently Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of amino acid residues 134-285 of SEQ ID NO:2, wherein the ~~polypeptide~~ protein having said first amino acid sequence ~~modulates~~ stimulates B lymphocyte proliferation, differentiation, or survival.

141. (Previously Presented) The method of claim 140 wherein the protein comprises a first amino acid sequence which is 95% or more identical to said second amino acid sequence.

142. (Previously Presented) The method of claim 140 wherein the protein also comprises a heterologous amino acid sequence.

143. (Previously Presented) The method of claim 142 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

144. (Previously Presented) The method of claim 140 wherein said protein is labeled.

145-146. (Cancelled)

147. (Previously Presented) The method of claim 140 wherein the immunodeficiency is common variable immunodeficiency (CVID).

148. (Cancelled)

149. (Previously Presented) The method of claim 140 wherein the immunodeficiency is Selective IgA deficiency.

150-211. (Cancelled)

212. (Currently Amended) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising administering to an individual, ~~a therapeutically~~ an effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the ~~polypeptide~~ protein having said amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2~~modulates lymphocyte proliferation, differentiation, or survival~~.

213. (Previously Presented) The method of claim 212 wherein the protein comprises amino acid sequence (a).

214. (Previously Presented) The method of claim 212 wherein the protein comprises amino acid sequence (b).

215. (Previously Presented) The method of claim 212 wherein the protein comprises amino acid sequence (c).

216. (Previously Presented) The method of claim 212 wherein the protein also comprises a heterologous amino acid sequence.

217. (Previously Presented) The method of claim 216 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

218. (Previously Presented) The method of claim 212 wherein said protein is labeled.

219-220. (Cancelled)

221. (Currently Amended) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising administering to an individual, ~~a therapeutically~~ an effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the ~~polypeptide~~ protein having said first amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2~~modulates lymphocyte proliferation, differentiation, or survival~~.

222. (Previously Presented) The method of claim 221 wherein the protein comprises amino acid sequence (a).

223. (Previously Presented) The method of claim 221 wherein the protein comprises amino acid sequence (b).

224. (Previously Presented) The method of claim 221 wherein the protein comprises amino acid sequence (c).

225. (Previously Presented) The method of claim 221 wherein the protein also comprises a heterologous amino acid sequence.

226. (Previously Presented) The method of claim 225 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

227. (Previously Presented) The method of claim 221 wherein said protein is labeled.

228-229. (Cancelled)

230. (Currently Amended) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising administering to an individual, a ~~therapeutically~~ effective amount of a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

231. (Previously Presented) The method of claim 230 wherein the protein is fused to a heterologous amino acid sequence.

232. (Previously Presented) The method of claim 231 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

233. (Previously Presented) The method of claim 230 wherein said protein is labeled.

234-274. (Cancelled)

275. (Previously Presented) The method of claim 89 wherein the immunodeficiency is common variable immunodeficiency (CVID).

276. (Previously Presented) The method of claim 89 wherein the immunodeficiency is Selective IgA deficiency.

277. (Previously Presented) The method of claim 98 wherein the immunodeficiency is common variable immunodeficiency (CVID).

278. (Previously Presented) The method of claim 98 wherein the immunodeficiency is Selective IgA deficiency.

279. (Previously Presented) The method of claim 107 wherein the immunodeficiency is common variable immunodeficiency (CVID).

280. (Previously Presented) The method of claim 107 wherein the immunodeficiency is Selective IgA deficiency.

281. (New) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising administering to an individual, an effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

282. (New) The method of claim 281 wherein the protein is fused to a heterologous amino acid sequence.

283. (New) The method of claim 282 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

284. (New) The method of claim 281 wherein said protein is labeled.

285. (New) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising contacting B lymphocytes with an effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

286. (New) The method of claim 285 wherein the protein comprises amino acid sequence (a).

287. (New) The method of claim 285 wherein the protein comprises amino acid sequence (b).

288. (New) The method of claim 285 wherein the protein comprises amino acid sequence (c).

289. (New) The method of claim 285 wherein the protein also comprises a heterologous amino acid sequence.

290. (New) The method of claim 289 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

291. (New) The method of claim 285 wherein said protein is labeled.

292. (New) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising contacting B lymphocytes with an effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said first amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

293. (New) The method of claim 292 wherein the protein comprises amino acid sequence (a).

294. (New) The method of claim 292 wherein the protein comprises amino acid sequence (b).

295. (New) The method of claim 292 wherein the protein comprises amino acid sequence (c).

296. (New) The method of claim 292 wherein the protein also comprises a heterologous amino acid sequence.

297. (New) The method of claim 296 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

298. (New) The method of claim 292 wherein said protein is labeled.

299. (New) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising contacting B lymphocytes with an effective amount of a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

300. (New) The method of claim 299 wherein the protein is fused to a heterologous amino acid sequence.

301. (New) The method of claim 300 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

302. (New) The method of claim 299 wherein said protein is labeled.

303. (New) A method of stimulating B lymphocyte proliferation, differentiation or survival comprising contacting B lymphocytes with an effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

304. (New) The method of claim 303 wherein the protein is fused to a heterologous amino acid sequence.

305. (New) The method of claim 304 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

306. (New) The method of claim 303 wherein said protein is labeled.

307. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising administering to an individual, an effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

308. (New) The method of claim 307 wherein the protein comprises amino acid sequence (a).

309. (New) The method of claim 307 wherein the protein comprises amino acid sequence (b).

310. (New) The method of claim 307 wherein the protein comprises amino acid sequence (c).

311. (New) The method of claim 307 wherein the protein also comprises a heterologous amino acid sequence.

312. (New) The method of claim 311 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

313. (New) The method of claim 307 wherein said protein is labeled.

314. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising administering to an individual, an effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said first amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

315. (New) The method of claim 314 wherein the protein comprises amino acid sequence (a).

316. (New) The method of claim 314 wherein the protein comprises amino acid sequence (b).

317. (New) The method of claim 314 wherein the protein comprises amino acid sequence (c).

318. (New) The method of claim 314 wherein the protein also comprises a heterologous amino acid sequence.

319. (New) The method of claim 318 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

320. (New) The method of claim 314 wherein said protein is labeled.

321. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising administering to an individual, an effective amount of a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

322. (New) The method of claim 321 wherein the protein is fused to a heterologous amino acid sequence.

323. (New) The method of claim 322 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

324. (New) The method of claim 321 wherein said protein is labeled.

325. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising administering to an individual, an effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

326. (New) The method of claim 325 wherein the protein is fused to a heterologous amino acid sequence.

327. (New) The method of claim 326 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

328. (New) The method of claim 327 wherein said protein is labeled.

329. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising contacting T lymphocytes with an effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

330. (New) The method of claim 329 wherein the protein comprises amino acid sequence (a).

331. (New) The method of claim 329 wherein the protein comprises amino acid sequence (b).

332. (New) The method of claim 329 wherein the protein comprises amino acid sequence (c).

333. (New) The method of claim 329 wherein the protein also comprises a heterologous amino acid sequence.

334. (New) The method of claim 333 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

335. (New) The method of claim 329 wherein said protein is labeled.

336. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising contacting T lymphocytes with an effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274-284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the protein having said first amino acid sequence can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2.

337. (New) The method of claim 336 wherein the protein comprises amino acid sequence (a).

338. (New) The method of claim 336 wherein the protein comprises amino acid sequence (b).

339. (New) The method of claim 336 wherein the protein comprises amino acid sequence (c).

340. (New) The method of claim 336 wherein the protein also comprises a heterologous amino acid sequence.

341. (New) The method of claim 340 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

342. (New) The method of claim 336 wherein said protein is labeled.

343. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising contacting T lymphocytes with an effective amount of a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

344. (New) The method of claim 343 wherein the protein is fused to a heterologous amino acid sequence.

345. (New) The method of claim 344 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

346. (New) The method of claim 343 wherein said protein is labeled.

347. (New) A method of stimulating T lymphocyte proliferation or differentiation comprising contacting T lymphocytes with an effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

348. (New) The method of claim 347 wherein the protein is fused to a heterologous amino acid sequence.

349. (New) The method of claim 348 wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

350. (New) The method of claim 347 wherein said protein is labeled.

REMARKS

For convenience, in the present response, Applicants will refer the Examiner to disclosure in the specification by referencing the appropriate paragraph numbers of the Substitute Specification that was submitted on May 3, 2002.

Status of the claims

Upon entry of the remarks and amendments, claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-350 will be pending in this application. Claims 281-350 have been added.

Claims 89, 98, 126, 140, 212, 221, and 230 have been amended. Applicants submit that the claims prior to amendments made herein were patentable and satisfied the requirements of 35 U.S.C. §§ 101, 102, 103 and 112. Applicants reserve the right to pursue the subject matter of the claims as recited prior to amendment herein in one or more continuing applications.

The word "therapeutically" has been deleted from claims 212, 221 and 230. The word "polypeptide" in claims 89, 98, 126, 140, 212 and 221 has been amended to "protein" because the term protein had antecedent basis in the claim.

In claims 212, 221, and 230, the words "modulates lymphocyte" have been replaced with the words "stimulates B lymphocyte." In claims 126 and 140, "lymphocyte" has been replaced with "B lymphocyte." New claims 281- 350 directed to methods of stimulating B cell proliferation, differentiation or survival or stimulating T cell proliferation differentiation by either administering proteins of the invention to an individual or contacting cells with proteins of the invention have been added. Support for these amendments may be found, for example, in the specification in paragraphs [0040], [0048]-[0051], [0077], [0153], [0156], [0300], [0620] and Examples 6 and 7.

Claims 89, 98, 212 and 221 have been amended to replace the phrase "modulates lymphocyte proliferation, differentiation or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Support for these amendments may be found, for example, in the specification in paragraphs [0331], [0342] – [0491] and Example 9.

No new matter has been added by way of amendment, and Applicants respectfully request entry of these amendments.

Objections to the Specification

In paragraph 3 of the Office Action mailed October 22, 2003, the Examiner objected to the Brief Description of the drawings for Figures 4A-4C for failing to make reference to the appropriate sequence identifier for the sequence of the HNEDU15 cDNA clone.

Applicants have amended paragraph [0060] to recite cDNA "clone HNEDU15" and to indicate that the nucleotide sequence obtained by sequencing the HNEDU15 clone is given in SEQ ID NO:1. Support for this amendment may be found in the specification as originally filed, for example in paragraphs [0023] and [0072] . Applicants submit these amendments address the Examiner's objections to the specification set forth in paragraph 3 of the Office action mailed October 22, 2003. Applicants respectfully request this objection be reconsidered and withdrawn.

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In response, Applicants draw the Examiner's attention to the Preliminary Amendment filed July 28, 2000 in which Applicants submitted 22 sheets of Formal Drawings containing each of the allegedly missing drawings. For the Examiner's convenience, copies of these 22 sheets of drawings as well as a copy of the date-stamped return receipt postcard indicating that these drawings were originally submitted to the United States Patent and Trademark Office on July 28, 2000 are submitted herewith. In view of the above, Applicants respectfully request that the Examiner withdraw the objections to the disclosure set forth in paragraphs 5-8 of the Office Action mailed October 22, 2003.

In paragraph 9 of the Office Action mailed October 22, 2003, the Examiner required that Applicants update the disclosure with respect to the status of patent application referenced in the disclosure.

The status of U.S. Application Serial Number 09/176,200 has been updated in paragraphs [0730] and [0731] to indicate its issuance as U.S. Patent No. 6,509,173. Applicants submit these amendments address the Examiner's objections to the specification set forth in paragraph 9 of the Office action mailed October 22, 2003. Applicants respectfully request this objection be reconsidered and withdrawn.

Enablement Under 35 U.S.C. §112, first paragraph

The Examiner maintains the rejection of claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-280 under 35 U.S.C. §112, first paragraph, for allegedly failing "to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention in scope with these claims." (see Paper No 17, page 5, lines 10-13).

The Examiner itemizes that methods which she believes to be enabled in this application at page 4, line 1 through page 5, line 9 of Paper No. 17. Applicants will address each item, in turn.

Item (I)

On page 4, lines 1-4, of Paper No. 17, the Examiner states, the specification is enabling for:

> **(I)** a method of stimulating B lymphocyte proliferation, differentiation or survival comprising administering to an individual, a therapeutically effective amount of a protein comprising amino acids 134-285 of SEQ ID NO:2, wherein said protein enhances B lymphocyte proliferation, differentiation or survival...

Claim 230, prior to amendments made herein, was directed to a method of stimulating lymphocyte proliferation, differentiation or survival comprising administering to an individual, a therapeutically effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2. Applicants have amended claim 230 to recite "B lymphocyte" rather than "lymphocyte". Additionally, Applicants have deleted the word "therapeutically" from claim 230 in the interest of clarity. The

Examiner acknowledges that the specification teaches that polypeptides comprising amino acids 134-285 of SEQ ID NO:2 have Neutrokine-alpha biological activities. (See, Paper No. 17, page 4, lines 1-5 and page 7, lines 9-12). Thus, Applicants submit that claim 230 (as amended) and claims dependent therefrom are in accordance with what, in item (I), the Examiner states satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph.

Applicants have also added new claim 281, similar to claim 230 as amended herein with the exception that the method recites use of a protein comprising (as opposed to "consisting of") amino acid residues 134-285 of SEQ ID NO:2. Accordingly, Applicants submit that claim 281 and claims dependent therefrom satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph.

Item (II)

On page 4, lines 9-13, of Paper No. 17, the Examiner states,

> The specification is also enabling for **(II)** a method of stimulating B lymphocyte proliferation, differentiation, and survival comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO: 2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2.

Claims 212 and 221, prior to amendments made herein, were directed to methods of stimulating lymphocyte proliferation, differentiation or survival using a protein that may not contain the entire amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2 wherein said protein modulates lymphocyte proliferation, differentiation or survival. Applicants have amended claim 212 and 221 to recite "B lymphocyte" rather than "lymphocyte" and to replace the phrase "modules lymphocyte proliferation, differentiation, or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Additionally, Applicants have deleted the word "therapeutically" from claims 212 and 221 in the interest of clarity. Thus, Applicants submit that amended claims 212 and 221 and claims dependent from said claims are in accordance with what, in item (II), the Examiner states satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph.

Applicants bring to the Examiner's attention that Applicants have added claims 285-306 which recite methods similar to the methods of claim 212-274 (as amended) and 281-284 with the exception that the phrase "administering to an individual, a therapeutically effective amount of...." is substituted with the phrase "contacting B lymphocytes with an effective amount of...." Applicants submit that claims 285-306 also satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph.

Item (III)

On page 4, lines 14-19, of Paper No. 17, the Examiner states,

> The specification is enabling for **(III)** a method of stimulating T lymphocyte proliferation and differentiation comprising administering to an individual, a therapeutically effective amount of (a) a protein comprising an amino acids 134-285 of SEQ ID NO: 2, wherein said protein enhances T lymphocyte proliferation or differentiation or (b) a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO:2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2.

Applicants have added new claims 307-350 directed to method of stimulating T lymphocyte proliferation or differentiation which parallel claims 212, 221, 230, 281, 285, 292, 299, 303 (as amended herein) and claims dependent from said claims. Accordingly, Applicants submit that claims 307-350, satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph.

Item (IV)

At page 4, line 20 to page 5, line 1 of Paper No. 17, the Examiner states the specification is being enabling for:

> **(IV)** a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising amino acids 134-285 of SEQ ID NO:2, wherein said protein enhances B lymphocyte proliferation, differentiation, or survival...

Prior to amendments made herein, claims 126 and 140 were directed to a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein consisting of/comprising a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of

amino acid residues 134-285 of SEQ ID NO:2, wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, differentiation, or survival. Applicants have amended these claims to recite "stimulates B lymphocyte" rather than "modulates lymphocyte". With respect to claims 107 and 113, the Examiner acknowledges that the specification teaches that polypeptides comprising amino acids 134-285 of SEQ ID NO:2 have Neutrokine-alpha biological activity (see Paper No. 17, page 4, lines 1-5 and page 7, lines 9-12). Thus, Applicants submit that amended claims 107, 113, 126, 140 and claims dependent from said claims are in accordance with what, in item (IV), the Examiner states satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph.

Item (V)

On page 5, lines 5-9, of Paper No. 17, the Examiner states,

> The specification is also enabling for **(V)** a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO: 2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2.

Claims 89 and 98, prior to amendments made herein, were directed to methods of treating an immunodeficiency using a protein that may not contain the entire amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2 wherein said protein modulates lymphocyte proliferation, differentiation or survival. Applicants have amended claims 89 and 98 to replace the phrase "modules lymphocyte proliferation, differentiation, or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Accordingly, Applicants submit that amended claims 89 and 98 and claims dependent from said claims are in accordance with what, in item (V), the Examiner states satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph.

Applicants believe they have addressed and overcome or obviated every aspect of this rejection of claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-280 under 35 U.S.C. §112, first

paragraph. Applicants further submit that all claims pending upon entry of the present amendment are in accordance with methods that the Examiner has stated are enabled by the present application. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Written Description Under 35 U.S.C. §112, first paragraph

Claims 89-95, 98-104, 107-110, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 stand rejected under 35 U.S.C. §112, first paragraph by the Examiner for alleged lack of written description. More specifically, the Examiner states that,

> The description of one neutrokine-alpha polypeptide species (SEQ ID NO: 2) particularly amino acids 134-285 of SEQ ID NO: 2, is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments of the neutrokine-alpha protein of SEQ ID NO:2 (Paper No. 17, page 11, lines 4-7.)

The Examiner contends that Applicants' description of the full-length polypeptide of SEQ ID NO:2 and of the biologically active, mature soluble form comprising amino acids 134-285 of SEQ ID NO:2 is insufficient to allow the skilled artisan to

> envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of making it. The protein itself is required. See *Fiers v. Revel* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. (Paper No. 17, page 11, lines 14-22)

The Examiner also states that the present case is not analogous to Example 14 of the Written Description Guidelines as Applicants have asserted.

Applicants respectfully disagree and submit that the case law the Examiner has cited does not support her position and that indeed, Example 14 is analogous to the present situation.

Both *Fiers* and *Amgen* involve situations in which parties asserted that a description of a DNA sequence was provided by disclosure of a method that could be used to obtain that DNA sequence. In *Fiers*, Appellant Revel was denied priority of invention back to an Israeli priority application because the Israeli priority application did not disclose the claimed invention - the complete DNA *sequence* coding for human fibroblast beta interferon, even though the same application disclosed a method for obtaining it. In *Amgen*, defendants Chugai tried to argue that Amgen's claims to a purified DNA sequence encoding human erythropoietin were anticipated by the work of the scientist who conceived of the method that was eventually used by Chugai to isolate that sequence even though that scientist, in fact, did not isolate the sequence of the EPO gene until after Amgen had identified the sequence. In both cases, the Federal Circuit held that in order to describe a claimed chemical structure such as a nucleotide sequence one must provide that chemical structure, i.e. that sequence.

Unlike in *Fiers* and *Amgen,* the present disclosure allows one of skill in the art to easily envision the entire genus of polypeptides recited in the claims because we have provided what was missing in *Fiers* and *Amgen*, *i.e.,* the chemical structure of the Neutrokine-alpha polypeptide as shown in SEQ ID NO:2. The *description* provided by the Applicants, *i.e.,* the sequence of the Neutrokine-alpha polypeptide, the nucleotide sequence encoding it (including access to the cDNA encoding Neutrokine-alpha deposited as ATCC accession Number 97768), and a description of the biological activity of Neutrokine-alpha, one of skill in the art can easily practice the claimed invention.

The Examiner, however, appears to believe that the written description requirement of 35 U.S.C. §112, first paragraph has not been satisfied because, aside from the full length polypeptide and polypeptides comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2, none of the remaining claimed fragments and variants were made and shown to have activity. (See, Paper No. 17, page 12, lines 4-5). Applicants maintain this is not what the law requires.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit recently re-emphasized the well-settled principle of law that "[t]he written description requirement

does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,'" *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). While the applicant must "blaze marks on trees," rather than "simply [provide] the public with a forest of trees," an Applicant is not required to explicitly describe each of the trees in the forest. *See Unocal*, 208 F.3d at 1000. *See also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement."). The Court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. Indeed, as the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Unocal*, 208 F.3d at 1001 (emphasis added).

The United States Patent and Trademark Office has published a *Synopsis of Application Written Description Guidelines* available from the USPTO website at http://www.uspto.gov/web/menu/written.pdf to assist Examiner's in evaluating whether an application satisfies the written description component of 35 U.S.C. §112, paragraph 1. Applicants assert that the scenario in Example 14 closely parallels that of the current application. The Examiner disagrees because it is her interpretation that in Example 14, the proteins and variants have a specific activity disclosed in the application, but in the present case, no activities have been experimentally demonstrated for the claimed polypeptides other than the full length sequence and polypeptides comprising 134-285 of SEQ ID NO: 2.

In Example 14 of the *Synopsis of Application Written Description Guidelines*, the hypothetical specification discloses the sequence of a protein that has a given functional activity, namely, catalyzing an enzymatic reaction. Example 14 of the USPTO Written Description Guidelines is described as follows: "The specification also **contemplates but does not exemplify variants of the protein**...The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the...activity of the protein." *Id.* at page 53 (emphasis added). The specification claims a protein comprising variants of the disclosed

protein that are at least 95% identical to SEQ ID NO:3 and are capable of catalyzing the enzymatic reaction.

Clearly, Example 14 indicates that only the full length polypeptide of SEQ ID NO:3 had been proven to have activity, while none of the variants have been proven to have activity, contrary to the Examiner's interpretation.

The USPTO analysis of the scenario in Example 14 is reproduced below:

> There is **actual reduction to practice of the single disclosed species**. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion:** The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention. (emphasis added).

If one merely substitutes "SEQ ID NO:3" with SEQ ID NO:2 of the present application and replaces "the specified catalytic activity" with the ability to "stimulate B lymphocyte proliferation, differentiation or survival" or to be "used to generate or select and antibody that specifically binds the polypeptide of SEQ ID NO:2" one is inevitably lead, by virtue of the reasoning set forth by the USPTO, to the conclusion that claims 89-95, 98-104, 107-110, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 meet the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicants submit that the specification conveys to one of skill in the art as of the earliest effective filing date of the present application, that Applicants were in possession of the claimed invention. Accordingly, Applicants submit that claims 89-95, 98-104, 107-110, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 fully meet the written description requirements of 35 U.S.C. § 112, first paragraph, and respectfully request that the Examiner's rejection of these claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

In paragraph 13 of the Office Action mailed October 22, 2003, the Examiner rejected claims 85-95, 98-104, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227 and 275-280 under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner pointed out that the word "polypeptide" in independent claims 89, 98, 126, 140, 212, and 221 did not have proper antecedent basis. Additionally, the Examiner asserted that the term "modulates" in claims 89, 98, 126, 140, 212, and 221 is unclear.

Applicants have amended each instance of "polypeptide" to "protein." The term "protein" has proper antecedent basis in these claims. Applicants thank the Examiner for bringing this error to their attention for correction.

While Applicants disagree that the term "modulates" is unclear, in the interest of facilitating prosecution in the present application, Applicants have amended each instance of "modulates" in claims to "stimulates."

Applicants submit these amendments address the Examiner's rejections under 35 U.S.C. §112, second paragraph set forth in paragraphs 12-15 of the Office action mailed October 22, 2003. Applicants respectfully request these rejections be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: January 22, 2004 Michele Shannon

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